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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/539,382	03/31/2000	Alison A. McCormick	LSB-001/CIP	9680

27860 7590 10/06/2005

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EXAMINER	
JOYCE, CATHERINE	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 10/06/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/539,382	MCCORMICK ET AL.	
	Examiner	Art Unit	
	Catherine M. Joyce	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *54,56,60-64,66,67,69,72,73 and 76-86* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *54,56,60-64,66,67,69,72,73 and 76-86* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

1. Claims 54,56,60-64,66,67,69,72,73 and 76-86 are pending and are under examination.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 77-80 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 77 recites the limitation "the tumor epitope" in part (iv). There is insufficient antecedent basis for this limitation in the claim and it is unclear what Applicant is intending to claim. Appropriate correction of the claims to clarify what is intended is required.

4. Claims 54,56,60-64,66,67,69,72,73,76 and 81-86 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In the recitation of "useful as a tumor-specific vaccine", it is unclear whether Applicant is claiming a polynucleotide useful as a tumor-specific vaccine for any tumor or a polynucleotide useful as a tumor-specific vaccine for a B-cell lymphoma tumor.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 54, 56, 60-64, 66, 72, 73, 76, 81-86 are rejected under 35 U.S.C. 103(a) as being unpatentable over Casper *et al* (1997, Blood 90(9):3699-3706), in view of Fiedler et al. (1997, Immunotechnology 3:205-216) and Shepherd (1995, Microbiology Reviews 59(4):548-578).

The claims are drawn to the following:

A polynucleotide comprising a nucleic acid sequence encoding a polypeptide epitope of a B-cell lymphoma surface immunoglobulin antigen useful as a tumor-specific vaccine in a subject with a tumor or at risk of developing a tumor, encoded at least in part by a nucleic acid in the cells of said tumor, and a nucleic acid sequence promoting expression of the polypeptide in a plant cell or plant and a nucleic acid sequence inducing transient replication of said polynucleotide in the cytoplasm, which polypeptide

includes an epitope or epitopes unique to, or overexpressed by, cells of said tumor, thereby distinguishing said tumor from all other tumors (i) of the same or different histological type, (ii) in said subject or in another member of said subject's species (claim 54),

Wherein the polypeptide comprises two V region domains of said immunoglobulin (claim 60),

Wherein the polypeptide comprises two V region domains of said immunoglobulin, wherein the two domains of the polypeptide are at least part of the V_H and at least part of the V_L domains of the immunoglobulin (claim 61),

Wherein the polypeptide comprises two V region domains of said immunoglobulin, wherein the two domains of the polypeptide are at least part of the V_H and at least part of the V_L domains of the immunoglobulin, wherein the part of the V_H region of said polypeptide includes at least one complementarity-determining region (CDR) (claim 62),

Wherein the polypeptide comprises two V region domains of said immunoglobulin, wherein the two domains of the polypeptide are at least part of the V_H and at least part of the V_L domains of the immunoglobulin, wherein the part of the V_H region of said polypeptide includes at least one complementarity-determining region (CDR), wherein the CDR of the polypeptide is CDR2 (claim 63),

Wherein the polypeptide comprises two V region domains of said immunoglobulin, wherein the two domains of the polypeptide are at least part of the V_H and at least part of the V_L domains of the immunoglobulin, wherein the polypeptide is a two-domain single chain antibody (scFV) that includes said at least part of the V_H and V_L domains (claim 64)

Wherein the polypeptide comprises two V region domains of said immunoglobulin, wherein the two domains of the polypeptide are at least part of the V_H and at least part of the V_L domains of the immunoglobulin, wherein the polypeptide is a two-domain single chain antibody (scFV) that includes said at least part of the VH and VL domains, wherein the domains of the polypeptide are linked by an amino acid linker that (a) has between one and about 50 residues; (b) consists of between one and 12

different amino acids, and (c) facilitates secretion and correct folding of the polypeptide to mimic the tumor epitope in its native form (claim 66);

and

A polynucleotide comprising a nucleic acid sequence encoding a polypeptide epitope of a B-cell lymphoma surface immunoglobulin antigen useful as a tumor-specific vaccine in a subject with a tumor or at risk of developing a tumor, encoded at least in part by a nucleic acid in the cells of said tumor, and a nucleic acid sequence of a vector capable of transiently replicating in the cytoplasm of and promoting expression of the polypeptide in a plant cell or plant, which polypeptide: includes an epitope or epitopes unique to, or overexpressed by, cells of said tumor, thereby distinguishing said tumor from all other tumors (i) of the same or different histological type, (ii) in said subject or in another member of said subject's species (claim 82),

Wherein said vector is a plant virus (claim 83),

Wherein said vector contains a subgenomic promoter capable of promoting expression of said polypeptide (claim 85),

Wherein said polypeptide is a two-domain single chain antibody (scFV) that includes the at least part of the V_H and the V_L domains (claim 86).

Caspar *et al* teach a polynucleotide sequence that encodes a single-chain antibody (scFV) derived from a B-cell lymphoma Ig surface antigen, wherein the scFV comprises two V region domains of the immunoglobulin, i.e. a V_H region and a V_L region (see figure 1 for example), and wherein the V_H region includes at least one CDR, particularly CDR2 (see page 3700). Furthemore, Caspar *et al* teaches that the V_H and V_L domains of the scFv are linked together by a linker sequence that is sixteen amino acids in length and that comprises two different amino acids (see page 3701). Caspar *et al.* teaches the expression of the expression of the scFV in insect cells to produce polypeptides (see page 3701). Caspar *et al.* also teaches that inoculation of mice with the scFV polypeptide resulted in an immune response, particularly a polyclonal anti-idiotypic antibody response (see page 3702).

Caspar *et al* teaches as set forth above but does not specifically a polynucleotide sequence that encodes a single-chain antibody (scFV) derived from a B-cell lymphoma Ig surface antigen in conjunction with a nucleic acid sequence that promotes expression of the polypeptide in a plant cell or plant and in conjunction with a nucleic acid sequence that induces transient replication of the polynucleotide in the cytoplasm.

Fiedler et al. teach that functionally active scFv proteins can be made and extracted from plants. Fiedler et al. also teaches the expression of scFV encoding mRNA using two plant expressible promoters, the CaMV 35S promoter and the USP promoter from *Vicia faba* (page 206). Fiedler et al. also specifically teaches the advantages of scFv production in plants in that high quantities of the scFV can be produced in plants, i.e. 4-6.8% of total soluble proteins (TSP) in leaves and 3-4% of TSP in tobacco seeds (abstract) and in that pharmaceutical production processes using plants offers several advantages in terms of there being no requirement for complex culture media or sterility of large culture vessels and no contamination risk with mammalian viruses or bacterial endotoxins (page 206).

Shepherd teaches the use of plant virus genomes as epichromosomal expression vectors for foreign genes (pages 565-571) and specifically teaches the advantages of such vectors in terms of the high copy number of replicating virus genomes per cell which potentially results in the high expression of an introduced gene, the ease of introduction and autonomous spread of the virus in plants, and the lack of positional effects (page 565). Shepherd also teaches that plant viral epichromosomal expression vectors have been employed to achieve high level expression of a foreign gene in an plant e.g. tobacco mosaic virus (TMV) (page 568). Shepherd also teaches the use of subgenomic promoters (page 558).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute the scFV plant production method of Fiedler et al. for the insect cell production method for single-chain antibody (scFV) derived from a B-cell lymphoma Ig surface antigen disclosed in Caspar, and thus to create a

polynucleotide comprising a nucleic acid sequence encoding a polypeptide epitope of a B-cell lymphoma surface immunoglobulin antigen and a nucleic acid sequence promoting expression of the polypeptide in a plant cell or plant. One of skill in the art would have been motivated to make the substitution of an epichromosomal expression vector because of the many advantages taught by Fiedler et al. for scFV expression in plant cells in terms of high protein yields, easier production methods, and lack of risk of contamination with mammalian viruses or bacterial endotoxins. One of skill in the art would have had a reasonable expectation of success in making the substitution because of the demonstrated success of plant production of scFV by Fiedler et al.

Furthermore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the plant production method for single-chain antibody (scFV) derived from a B-cell lymphoma Ig surface antigen of the combined references in combination with a plant virus genome epichromosomal expression vector as taught in Shepherd, and thus to create a polynucleotide comprising a nucleic acid sequence encoding a polypeptide epitope of a B-cell lymphoma surface immunoglobulin antigen, a nucleic acid sequence promoting expression of the polypeptide in a plant cell or plant, and a nucleic acid sequence inducing transient replication of the polynucleotide in the cytoplasm. One of skill in the art would have been motivated to make the substitution because of the many advantages taught by Shepherd in terms of the potential for high expression of an introduced gene and the ease of introduction and autonomous spread of the virus vector in plants, and the lack of positional effects. One of skill in the art would have had a reasonable expectation of success in making the substitution because of the stated success in Shepherd of high level foreign protein production using an epichromosomal tobacco mosaic virus vector.

7. Claims 67 and 77 are rejected under 35 U.S.C. 103(a) as being unpatentable over Casper *et al* (1997, Blood 90(9):3699-3706), in view of Fiedler et al. (1997, Immunotechnology 3:205-216) and Shepherd (1995, Microbiology Reviews 59(4):548-

578), and further in view of Tang et al. (1996, J. Biol. Chem. 271(26):15682-15686) and US Patent No. 5,571,698.

The claims are as follows:

A polynucleotide comprising a nucleic acid sequence encoding a polypeptide epitope of a B-cell lymphoma surface immunoglobulin antigen useful as a tumor-specific vaccine in a subject with a tumor or at risk of developing a tumor, encoded at least in part by a nucleic acid in the cells of said tumor, and a nucleic acid sequence promoting expression of the polypeptide in a plant cell or plant and a nucleic acid sequence inducing transient replication of said polynucleotide in the cytoplasm, which polypeptide includes an epitope or epitopes unique to, or overexpressed by, cells of said tumor, thereby distinguishing said tumor from all other tumors (i) of the same or different histological type, (ii) in said subject or in another member of said subject's species,

Wherein the polypeptide comprises two V region domains of said immunoglobulin, wherein the two domains of the polypeptide are at least part of the V_H and at least part of the V_L domains of the immunoglobulin, wherein the polypeptide is a two-domain single chain antibody (scFV) that includes said at least part of the VH and VL domains, wherein the domains of the polypeptide are linked by an amino acid linker that (a) has between one and about 50 residues; (b) consists of between one and 12 different amino acids, and (c) facilitates secretion and correct folding of the polypeptide to mimic the tumor epitope in its native form, wherein the linker of said polypeptide is a member of a randomized library of linkers that vary in size and sequence, and the library is encoded by nucleic acid sequences consisting of a repeated pattern of degenerate repeated triplet nucleotides having the following requirements; (i) position 1 of each repeated triplet cannot be the same nucleotide as position 2 of the repeated triplet; (ii) position 2 of each repeated triplet cannot be the same nucleotide as position 3 of the repeated triplet; *or* position 1 of each repeated triplet cannot be the same nucleotide as position 3 of the repeated triplet (claim 67);

and

A polynucleotide encoding a two domain single chain antibody (scFV) wherein a first domain is linked to a second domain by an amino acid linker that (ii) has between one and about 50 residues; (iii) consists of between one and 12 different amino acids; (iv) facilitates secretion and correct folding of said polypeptide to mimic the tumor epitope in its native form in or on said tumor cell; (v) is a member of a randomized library of linkers that vary in size and sequence, and said library is encoded by nucleic acid sequences consisting of a repeated pattern of degenerate repeated triplet nucleotides having the following requirements, a) position 1 of each repeated triplet cannot be the same nucleotide as position 2 of the repeated triplet; b) position 2 of each repeated triplet cannot be the same nucleotide as position 3 of the repeated triplet; c) or position 1 of each repeated triplet cannot be the same nucleotide as position 3 of the repeated triplet (claim 77).

Casper et al., Fiedler et al. and Shepherd teach as set forth above but do not teach a linker that is a member of a randomized library of linkers that vary in size and sequence, wherein the library is encoded by nucleic acid sequences consisting of a repeated pattern of degenerate repeated triplet nucleotides having the following requirements; (i) position 1 of each repeated triplet cannot be the same nucleotide as position 2 or the repeated triplet; (ii) position 2 of each repeated triplet cannot be the same nucleotide as position 3 of the repeated triplet; or (iii) position 1 of each repeated triplet cannot be the same nucleotide as position 3 of the repeated triplet.

Tang et al. teaches that when the use of conventional linkers fails to achieve the desired functionality with an scFV, randomized linkers may be employed to allow for the selection of a functional linker from a large population of candidate sequences (page 15682).

US Patent No. 5,571,698 teaches that a method for generating random variability in protein is to use variegated or degenerate codons, wherein particular variegated

codons described are, for example, SNT, RNG, RMG, VNT, RRS, NNT, NNG (column 39, lines 1-37) or VNS, RRS, NHT (column 44, lines 48-65) or NWT, VYT, NNK, VWG or NAS (column 163, lines 28-39) that are degenerate wherein M is A or C, R is A or G, W is A or T, S is C or G, Y is T or C, K is G or T, V is A or C, or G, H is A, C or T, D is A, G or T, B is C, G or T, and N means any base (column 166). US 5,571,698 teaches the benefits of using controlled random mutagenesis to minimize the number of stop codons or to created preferred amino acid substitution sets such as equalizing the number of acidic and basic amino acid residues (column 6, lines 1-14). U.S. Patent 5,571,698 also teaches the use of a series of repeated degenerate codons to generate random peptides (column 5, line 47 thru column 6, line 15).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the plant production method for single-chain antibody (scFV) derived from a B-cell lymphoma Ig surface antigen of the combined references in combination with a randomized linker as taught by Tang et al., wherein the randomization process was controlled by using a repeated set of degenerate nucleotides as taught by US Patent 5,571,698. The degenerate codons suggested in US Patent 5,571,698 include codons wherein position 1 of each repeated triplet cannot be the same nucleotide as position 3 of the repeated triplet, e.g. degenerate codons VNT, VYT, SNT, or wherein position 2 of each repeated triplet cannot be the same nucleotide as position 3 of the repeated triplet, e.g. degenerate codons RMG, VWG, NAS. One of skill in the art would have been motivated use a random linker as taught by Tang because of the advantages taught by Tang in maximizing functionality of an scFV using randomized linkers. One of skill in the art would have had a reasonable expectation of success because of the success demonstrated in Tang with the use of randomized linkers. One of skilled in the art would have motivated to employ the controlled randomization taught by US Patent 5,571,698 via the use of degenerate triplet codons, and would have had a reasonable expectation of success in doing so, because of the advantages taught by US Patent 5,571,698 in terms of eliminating stop codons or achieving a balanced set of amino acid substitutions because.

8. It is noted that limitations in the claim that are drawn to intended uses of the polynucleotide, or to intended uses of the polypeptide encoded by the polynucleotide are not given weight for purposes of comparing the claims with the prior art.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Catherine M. Joyce whose telephone number is 571-272-3321. The examiner can normally be reached on Monday thru Friday, 10:15 - 6:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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10/3/05